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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
087986,568	12/05/97	BACH	J 040388/0110

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EXAMINER

VANDER VEGT, F

ART UNIT

PAPER NUMBER

1644

DATE MAILED:

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.
08/986,568

Applicant(s)
Bach et al

Examiner
F. Pierre VanderVegt

Group Art Unit
1644



☒ Responsive to communication(s) filed on Dec 22, 1998

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire three month(s), ~~or thirty days, whichever is longer~~, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1, 2, 4-7, 9-13, and 16-18 ~~is/are~~ pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1, 2, 4-7, 9-13, and 16-18 ~~is/are~~ rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been
☐ received.

☐ received in Application No. (Series Code/Serial Number) _____

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Claims 3, 8, 14 and 15 have been canceled.

New claims 16-18 have been added.

Claims 1, 2, 4-7, 9-13, 14 and 16-18 are currently pending in this application.

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1. In view of the amendment filed December 22, 1998, only the following rejections are maintained.

Claim Rejections - 35 U.S.C. § 102

- 10 The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

- 15 2. Claims 1-2, 4-5, 9, 13 and 16-18 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Chatenoud et al (A5 on form PTO-1449), as evidenced by Hughes et al (A4), both of record.

20 The Chatenoud et al reference teaches the induction of antigen-specific unresponsiveness in NOD mice with full-blown disease (Abstract in particular), by injection of non-mitogenic anti-CD3 monoclonal antibody (mAb) F(ab')₂ fragments (page 123, subsection "Mice and Antibodies in particular), resulting in complete remission of overt disease (Abstract in particular). Although it is not specifically stated by Chatenoud et al, it is a fact well known in the art that F(ab')₂ fragments are non mitogenic because they do not induce the release of cytokines like intact mAbs do, as evidenced by Hughes et al's teachings using the same hamster monoclonal antibody, 2C11, 25 for treatment in an unrelated autoimmune disease model (page 324, column 2 in particular). Chatenoud et al also teaches that the production of the anti-CD3 monoclonal antibody F(ab')₂ fragments is by "conventional pepsin digestion of the entire antibody molecule" (page 123, subsection "Mice and Antibodies in particular). The prior art teaching clearly anticipates the claimed invention.

- 30 Applicant's arguments filed December 22, 1998 have been fully considered but they are not persuasive.

Applicant argues that the Chatenoud et al reference is not applicable as an anticipatory reference because Chatenoud et al teaches “immunosuppression” rather than “unresponsiveness” as taught by the instant specification and that the teachings of Chatenoud et al are not antigen-specific, while those of the instant specification are antigen specific. The Examiner respectfully disagrees with this position. Applicant’s characterization of Chatenoud et al constitutes a piecemeal analysis of the reference, carefully choosing phrases out of the reference in order to support the argument. “Immunosuppression” is a broad term which includes not only partial amelioration of a condition, as Applicant appears to suggest, but also encompasses the induction of a nonresponsive state to antigens which are the object of an active immune response in a subject. It is respectfully submitted that the latter is the meaning one skilled in the art would interpret as the usage of the term by Chatenoud et al. Chatenoud et al teaches that anti-CD3 antibodies administered to adult female NOD mice within 7 days of the onset of full-blown diabetes induced a complete remission of overt disease evidenced by a return to permanent normoglycemia in 64-80% of mice treated. Chatenoud et al further teaches that the remission was durable, lasting more than 4 months (Abstract in particular). Chatenoud et al also teaches that self-tolerance can be restored in adult mice once autoimmunity is fully established using such an anti-CD3 regimen (Abstract in particular). Regarding Applicant’s contention that Chatenoud et al’s teachings are not antigen-specific, Applicant is again invited to note the Abstract, where Chatenoud et al clearly states that the lack of immune response was specific for β cell antigens, as treated mice rejected histoincompatible skin grafts normally while retaining syngeneic islet grafts, showing that the nonresponsiveness induced by the treatment taught by Chatenoud et al was not a generalized state of immune suppression. What Chatenoud et al effectively demonstrates therefore is a working of the two-signal hypothesis, wherein the responsive T cells are permitted to recognize the target antigen but are deprived of the secondary signal by the anti-CD3 reagent, preventing function of the cell and inducing a lasting state of anergy or nonresponsiveness. Furthermore, it is noted that the data presented in the working example of the instant disclosure is no different than the data presented in Chatenoud et al, therefore it would be impossible to interpret the data of the instant disclosure differently, i.e., antigen-specific versus non-antigen-

specific tolerance, from that taught by Chatenoud et al. Regarding Applicant's contention with the evidentiary nature of the Hughes et al reference, the Examiner respectfully submits that Applicant has misunderstood the nature of the reference. Hughes et al was cited solely to illustrate the knowledge in the art that F(ab')² fragments of anti-CD3 are non-mitogenic, whereas intact anti-CD3 antibodies induce cytokine release. New claims 17 and 18 are included in this ground of rejection because the mere recitation of a dosage range does not render the claimed invention patentably distinct, as it would be well within the purview of an ordinary practitioner to determine appropriate doses for treatment of a human patient based upon the murine model data of Chatenoud et al.

Claim Rejections - 35 U.S.C. § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office Action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the Examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the Examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

3. Claims 1-2, 4-7, 9-13 and 16-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Racadot et al (U on form PTO-892) in view of Güssow et al (V) and Chatenoud et al (A5).

Chatenoud et al has been discussed supra. Chatenoud et al does not teach murine mAbs, humanized mAbs or the treatment of multiple sclerosis. Racadot et al teaches the treatment of multiple sclerosis in human patients with a dosage of 5 mg/day of a murine monoclonal antibody designated muromonab-CD3, a.k.a. OKT-3 (page 201, subsection 1.2.3 in particular). Racadot et al also teaches that the treatment is associated with a dramatic decrease in T cell count and the

induction of clonal anergy (page 202, first new paragraph in column 2 in particular). However, Racadot et al teaches a drawback in the treatment in that all patients developed anti-murine Abs and some patients deteriorated during therapy (page 201, subsection 1.2.3 in particular) and a massive cytokine release (page 203, section 3 in particular). The skilled artisan would have readily recognized that the massive cytokine release associated with muromonab-CD3 treatment could be averted through the use of F(ab')₂ fragments of the mAb as taught by Chatenoud et al. The skilled artisan would have further recognized this still leaves the obstacle of the generation of anti-murine Abs in the patient because Güssow et al teaches that anti-murine Abs are still generated to the murine framework regions which remain in murine-human chimeric Abs (pages 99-100 in particular), which are essentially murine F(ab')₂ fragments fused to a human Fc region. Güssow et al teaches that this problem can be overcome by reshaping, humanization, of the murine Ab. It would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made to modify the effective muromonab-CD3 mAb by humanization as taught by Güssow et al in order to alleviate the anti-murine complications taught by Racadot et al. One would have been further motivated to modify the humanized muromonab-CD3 by pepsin digestion of the entire humanized antibody to generate F(ab')₂ fragments to use for treatment as taught by Chatenoud et al in order to eliminate the massive cytokine release associated with treatment using intact anti-CD3 antibodies. One would have been motivated to combine these references with a reasonable expectation of success by the teachings of Racadot et al and Chatenoud et al that anti-CD3 treatment induces tolerance in an ongoing autoimmune reaction and by the teachings of Chatenoud et al and Güssow et al which address the problems taught to be associated with intact muromonab-CD3 treatment by Racadot et al. Claim 6 is included because highly purified, endotoxin free reagents are routinely prepared in the art and are a well-known requirement for treatment of human patients. Claims 10 and 11 are included because, while none of the cited references specifically teach the treatment of rheumatoid arthritis or psoriasis, the anti-CD3 course of treatment does not require the administration of disease specific antigens or agents to the subject, nor is there a requirement of knowledge of the target antigen in the disease. Therefore, the skilled artisan would be able to reasonably predict that the method would be useful for the treatment of any autoimmune condition in which the involvement of T lymphocytes is a major factor in the etiology of the disease.

In response to Applicant's argument that there is no suggestion to combine the references, the Examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art (emphasis added). See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Applicant argues against the prior art applied in this ground of

rejection on several fronts, none of which are persuasive. First of all, Applicant again protests the inclusion of Chatenoud et al on the grounds that Chatenoud et al's teachings are not antigen-specific in the tolerance induced by the taught method. This particular point has been discussed at length supra. Applicant has not provided any further argument regarding the teachings of

5 Racadot et al and Güssow et al. Second, Applicant's argument that the endotoxin free reagents [claim 6] are not a "well-known requirement" for administration to a human subject without the guidance of the instant disclosure is without merit. It is general knowledge in the art that the presence of endotoxins in a treatment composition can be detrimental to the well-being of subject.

10 Endotoxin is well known in the art to be associated with septic shock, wherein an exaggerated cytokine response is associated with an acute production of $\text{TNF}\alpha$, IL-1 and IL-12 which stimulates a subsequent rise in $\text{IFN}\gamma$ with potentially lethal consequences. The prior art does not need to teach elements which are common sense practices in the art. Third, Applicant urges that a skilled artisan could not reasonably predict from the combination of the prior art teachings that a

15 F(ab')_2 fragment of a humanized anti-CD3 antibody could be used to treat other autoimmune conditions in which the involvement of T lymphocytes is a major factor in the etiology of the disease. The Examiner respectfully disagrees with this position. Racadot et al shows that the same anti-CD3 antibody used by Chatenoud et al to treat diabetes can be used to treat unrelated autoimmune diseases such as multiple sclerosis. However, Racadot et al teaches that there were two problems with using the intact murine monoclonal antibody, cytokine release and human anti-

20 mouse antibody (HAMA) generation in the patient. Chatenoud et al teaches that the use of F(ab')_2 fragments alleviates the problem of cytokine release. Because the F_c portion of the molecule has been removed, F_c receptor bearing cells will not be able to bind the antibodies immobilized on the surface of the CD3^+ cells and thus will not be stimulated to release cytokines.

25 However, the F(ab')_2 fragments still have murine framework regions supporting the antigen-binding variable regions and Güssow et al teaches that these regions are sufficient for inducing a HAMA response in a patient. Güssow et al also teaches that this problem can be alleviated by humanizing the antibody, thereby replacing the murine framework regions with human. F(ab')_2 fragments of the humanized anti-CD3 would still be necessary, as the human F_c would also be

likely to stimulate cytokine release. Therefore, sufficient motivation exists to combine the teachings of Chatenoud et al, Racadot et al and Güssow et al both in the references themselves and in the knowledge generally available to the artisan of ordinary skill at the time the invention was made. New claims 17 and 18 are included in this ground of rejection because the mere
5 recitation of a dosage range does not render the claimed invention patentably distinct, as it would be well within the purview of an ordinary practitioner to determine appropriate doses for treatment of a human patient based upon the murine model data of Chatenoud et al.

Conclusion

10 4. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after
15 the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

20 5. Papers related to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. Papers should be faxed to Group 1640 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The fax phone number for official
25 documents to be entered into the record for Art Unit 1644 is (703)305-3014.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to F. Pierre VanderVegt, whose telephone number is (703)305-6997. The Examiner can normally be reached Tuesday through Friday and even-numbered Mondays (on 1999 365-day calender) from 7:00 am to 4:00 pm ET. A message may be left on the Examiner's
30 voice mail service. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ms. Christina Chan can be reached at (703)308-3973. Any inquiry of a

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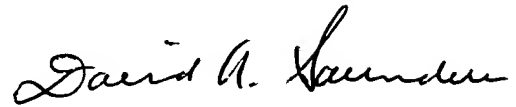
general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist, whose telephone number is (703)308-0196.

January 26, 1999

5 F. Pierre VanderVegt, Ph.D.

Patent Examiner

Art Unit 1644



DAVID SAUNDERS
PRIMARY EXAMINER
ART UNIT ~~182~~ / 644